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EXAMINER
RAMIREZ, DELIA M

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 09/09/2003 11

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application N .	Applicant(s)	
	09/966,742	DOEKEL ET AL.	
	Examiner	Art Unit	
	Delia M. Ramirez	1652	

-- The MAILING DATE of this communication appears on the c ver sheet with the c rresp ndence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 August 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-25* is/are pending in the application.

4a) Of the above claim(s) *14-25* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-13* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *7* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Status of the Application

Claims 1-25 are pending.

It is noted that the examination of the instant application has been assigned to a different Examiner in Group Art Unit 1652.

Applicant's election with traverse of Group I, claims 1-13 drawn to a method for the microbiological production of Asp-Phe from L-Asp and L-Phe, in Paper No. 10, filed on 8/1/2003 is (are) acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 14-25 are withdrawn from further consideration by the Examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Specification

1. The specification is objected for not complying with sequence rules. See, for example, page 33, lines 30-34. Applicant is required to insert sequence identifiers in front of sequences referred to in the specification (37 CFR 1.821(d)). Appropriate correction is required.

2. The specification is objected to due to the presence of a blank space in page 21. Appropriate correction is required.

Priority

3. Acknowledgment is made of a claim for domestic priority under 35 U.S.C. 119(e) to provisional application No. 60/133,402 filed on 05/10/1999.

4. Acknowledgment is made of a claim for foreign priority under 35 U.S.C. 119(a)-(d) to EUROPEAN PATENT OFFICE (EPO) 99200954.8 filed on 03/29/1999, and EUROPEAN PATENT OFFICE (EPO) 99203518.8 filed on 10/26/1999.

5. Acknowledgment is made of a claim for domestic priority under 35 U.S.C. 120 or 121 to PCT/NL00/00206 filed on 03/28/2000.

Information Disclosure Statement

6. The information disclosure statement (IDS) submitted on 1/23/2002 is acknowledged. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner.

Claim Objections

7. Claims 1-13 are objected to because of the following informalities: it is suggested that the term "Method for..." be replaced with "A method for..". Appropriate correction is required.

8. Claim 1 is objected to because of the following informalities: the term "containing thiolation domain" should be replaced with "a thiolation domain". Appropriate correction is required.

9. Claims 6-10 and 13 are objected to because of the following informalities: it is suggested that the term "micro-organism" be replaced with "microorganism". Appropriate correction is required.

10. Claims 6 and 8 are objected to because of the following informalities: it is suggested that semicolons (;) be replaced with commas (,). Appropriate correction is required

11. Claim 11 is objected to because of the following informalities: the term "mixtures thereof is being fed" should be "mixtures thereof are being fed". Appropriate correction is required.

Claim Rejections - 35 USC § 112, Second Paragraph

12. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

13. Claims 1-13 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

14. Claim 1 (claims 2-5 and 11-12 dependent thereon) is indefinite in the recitation of "method for the microbiological production of ..." for the following reasons. The term "microbiological production" implies the use of microbes in the production of Asp-Phe as recited. However, as written, there is no step which indicates the use of a microbe in the production of Asp-Phe. For examination purposes, no patentable weight will be given to the term "microbiological". Correction is required.

15. Claim 1 (claims 2-13 dependent thereon) is indefinite in the recitation of "comprising two minimal modules connected by one condensation domain, wherein the N-terminal module of

these modules is recognizing L-aspartic acid and the C-terminal module of these modules is recognizing L-phenylalanine and is covalently bound at its N-terminal end to the condensation domain ....and that the α-L-aspartyl-L-pheynylalanine (Asp-Phe) formed is recovered" for the following reasons. First, the terms "N-terminal module of these modules" and "C-terminal module of these modules" are unclear as one cannot determine if the term "of these modules" refers to other modules in addition to the minimal modules recited in the claim or if it refers to the dipeptide synthetase complex. Furthermore, the term "is covalently bound at its N-terminal end" is unclear as one cannot determine what is covalently bound to the condensation domain (i.e. which minimal module is covalently bound to the condensation domain). Moreover, the term "and that the.....formed is recovered" is unclear since one cannot find the correlation between such term and what is being recited previously in the claim. For examination purposes, it will be assumed that the claim is directed to a method for the production of Asp-Phe from L-Asp and L-Phe wherein said method comprises the steps of: (a) contacting the substrates in the presence of ATP with a non-ribosomal dipeptide synthetase comprising two minimal modules connected by one condensation domain, wherein the N-terminal module of the non-ribosomal dipeptide synthetase recognizes L-Asp and the C-terminal module of the non-ribosomal dipeptide synthetase recognizes L-Phe, wherein each of these minimal modules is composed of an adenylation domain and a 4'-phophopantetheinyl cofactor containing a thiolation domain; and (b) recovering the Asp-Phe produced in (a). Correction is required.

16. Claim 2 is indefinite in the recitation of "wherein the condensation domain in the dipeptide synthetase is connected to both minimal modules in such a way that it is also covalently bound to the module recognizing L-aspartic acid" for the following reasons. As

indicated above in regard to claim 1, it is unclear as to what is "covalently bound at its N-terminal end to the condensation domain", therefore, one cannot clearly determine how the limitation "also covalently bound to the module recognizing L-aspartic acid" further narrows the scope of the claim. For examination purposes, it will be assumed that both minimal modules, are covalently bound to the condensation domain. Correction is required.

17. Claim 3 is indefinite in the recitation of "method for....., further comprising a thioesterase-like releasing factor..." for the following reasons. Claim 3 is directed to a method, therefore it is unclear as to how a method can comprise a releasing factor. Furthermore, the term "thioesterase-like" is unclear since one cannot determine what is encompassed by the term "like". For examination purposes, it will be assumed that the intended meaning of the term is "wherein the non-ribosomal dipeptide synthetase further comprises a thioesterase releasing factor for the Asp-Phe formed". Correction is required.

18. Claim 4 is indefinite in the recitation of "method for..., wherein the thioesterase-like releasing factor forms an integrated domain of the dipeptide synthetase at the C-terminus thereof" for the following reasons. First, there is no antecedent basis for the releasing factor. In addition, the term "integrated domain" is confusing since one cannot establish the meaning of the term "integrated" within the context of the claim and the specification does not provide a definition of the term. As written, one cannot determine if integrated domain refers to a domain which is structurally part of the same polypeptide comprising the C-terminus of the dipeptide synthetase or if it is a separate protein (i.e. separate polypeptide) which binds to the C-terminus of the dipeptide synthetase via, for example, H-bonding. Furthermore, the term "thioesterase-like" is unclear since one cannot determine what is encompassed by the term "like". For

examination purposes, it will be assumed that claim 4 is directed to the method of claim 3 wherein the releasing factor is a domain which is in the same polypeptide comprising the C-terminus of the dipeptide synthetase. See above for interpretation of claim 3. Correction is required.

19. Claim 5 (claim 6-10 dependent thereon) is indefinite in the recitation of "wherein a non-integrated protein with thioesterase Type II-like activity" for the following reasons. The term "non-integrated protein" is unclear and confusing since one cannot determine the meaning of the term within the context of the claim and the specification does not provide a clear definition of the term either. As written, one cannot determine if a non-integrated protein is a completely separate protein which does not associate with the dipeptide synthetase or if it is a separate protein which is capable of some interaction with the dipeptide synthetase, such as H-bonding. Furthermore, it is unclear what is encompassed by the term "like". For examination purposes, it will be assumed that the term recites "wherein a protein having thioesterase Type II activity". Correction is required.

20. Claim 6 (claims 7-10 dependent thereon) is indefinite in the recitation of "synthetase is present in living cell-material of a micro-organism; glucose, L-Asp, L-Phe, or mixtures thereof are being fed to said fermentor; and the Asp-Phe formed is recovered" for the following reasons. First, it is unclear what the meaning of the term "living cell-material of a micro-organism" is. Furthermore, there is no antecedent basis for "said fermentor". In addition, the term "and the Asp-Phe formed is recovered" is redundant since this step has already being recited in claim 1, from which claim 6 is dependent. For examination purposes, it will be assumed that the claim is

directed to the method of claim 5 wherein the synthetase is present in a microorganism. Correction is required.

21. Claim 7 (claim 8 dependent thereon) is indefinite in the recitation of "wherein the micro-organism is first grown in a fermentor...and feeding of the glucose.....is started" for the following reasons. It is unclear as to the correlation between the term "feed of the glucose..is started" and what is being recited previously. For examination purposes, it will be assumed that the intended meaning of the term is "wherein the microorganism is first grown in a fermentor to reach a predetermined cell density before the expression of the Asp-Phe dipeptide synthetase is switched on, and wherein glucose, L-Asp, L-Phe, or mixtures thereof are added at the same time the expression of the Asp-Phe dipeptide synthetase is switched on". Correction is required.

22. Claim 11 (claims 12-13 dependent thereon) is indefinite in the recitation of "wherein the production of Asp-Phe is carried out in vitro in an enzyme reactor, while ATP is supplied, L-Asp, L-Phe, or mixtures thereof is being fed, and the Asp-Phe formed is recovered" for the following reasons. As written, it is unclear as to whether there is a limitation in regard to when ATP is supplied and whether ATP is fed at the same time as L-Asp, L-Phe or mixtures thereof. Furthermore, the term "and the Asp-Phe formed is recovered" is redundant since this step has already being recited in claim 1, from which claim 11 depend. In addition, the term "enzyme reactor" is unclear since one cannot determine the meaning of the term within the context of the claim. As written, one cannot establish if the production of Asp-Phe is carried out such that all the enzymes required are provided without the need to use a microorganism. For examination purposes, it will be assumed that claim 11 is directed to the method of claim 1 wherein the

production of Asp-Phe is carried out in the absence of microorganisms, and wherein ATP and L-Asp, L-Phe, or mixtures thereof, are fed simultaneously. Correction is required.

Claim Rejections - 35 USC § 112, First Paragraph

23. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

24. Claims 1-13 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1-2, 6-13 are directed to a method for the production of Asp-Phe wherein a genus of non-ribosomal dipeptide synthetases is used. Claims 3 and 4 add the limitation that the method also uses a genus of thioesterase releasing factors in addition to the genus of dipeptide synthetase. Claim 5 adds the limitation that the method also uses a genus of thioesterase Type II proteins along with the genus of dipeptide synthetase. While the specification discloses the production of Asp-Phe using (1) a hybrid Asp-Phe dipeptide synthetase encoded by a DNA wherein part of the srfB gene from B subtilis ATCC 21332 and DNA from B. brevis ATCC 8185 coding for a Phe minimal module (adenylation (A) and thiolation (T) domain) are used, and (2) a hybrid as described in (1) further comprising what appears to be a thioesterase domain from B. subtilis ATCC 21332, the specification is silent in regard to (a) the structures of other Asp or Phe

minimal modules and their components, i.e. adenylation domains and thiolation domains, (b) the structures of other thioesterases or thioesterases type II proteins, (c) the structures of other condensation domains, (d) which combinations are likely to result in hybrid Asp-Phe dipeptide synthetases which can be used in the claimed method, (e) the critical structural elements required in a dipeptide synthetase to specifically synthesize Asp-Phe or to display thioesterase type II activity, or (f) the critical structural elements required in a polypeptide to be a thioesterase releasing factor.

While the argument can be made that the genera of dipeptide synthetases, thioesterase releasing factors, and thioesterase type II proteins required to practice the claimed method are adequately described since such proteins can be isolated/made by sequence comparison using the structures disclosed in the instant application or those of the prior art, the state of the art teaches that sequence comparison alone should not be used to determine a protein's function and that small amino acid changes can drastically change the function of a polypeptide. Bork (Genome Research, 10:398-400, 2000) teaches protein function is context dependent, and both molecular and cellular aspects must be considered (page 398). Witkowski et al. (Biochemistry 38:11643-11650, 1999) teaches that one amino acid substitution transforms a β-ketoacyl synthase into a malonyl decarboxylase and completely eliminates β-ketoacyl synthase activity. Van de Loo et al. (Proc. Natl. Acad. Sci. 92:6743-6747, 1995) teaches that polypeptides of approximately 67% homology to a desaturase from *Arabidopsis* where found to be hydroxylases once tested for activity. Seffernick et al. (J. Bacteriol. 183(8):2405-2410, 2001) teaches that two naturally occurring Pseudomonas enzymes having 98% amino acid sequence identity catalyze two different reactions: deamination and dehalogenation, therefore having different function. Broun

et al. (Science 282:1315-1317, 1998) teaches that as few as four amino acid substitutions can convert an oleate 12-desaturase into a hydrolase and as few as six amino acid substitutions can transform a hydrolase to a desaturase. The specification only discloses two hybrid Asp-Phe dipeptide synthetases which is insufficient to put one of ordinary skill in the art in possession of all attributes and features of all species within the genera required to practice the claimed method. Thus, one skilled in the art cannot reasonably conclude that Applicant had possession of the claimed invention at the time the instant application was filed.

25. Claims 1-13 rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for the production of Asp-Phe using (1) a hybrid Asp-Phe dipeptide synthetase encoded by a DNA wherein part of the srfB gene from B subtilis ATCC 21332 and DNA from B. brevis ATCC 8185 coding for a Phe minimal module (adenylation (A) and thiolation (T) domain) are used, and (2) a hybrid as described in (1) further comprising a thioesterase domain from B. subtilis ATCC 21332, does not reasonably provide enablement for a method for the production of Asp-Phe using (a) any Asp-Phe dipeptide synthetase comprising any adenylation, thiolation and condensation domain, or (b) any Asp-Phe dipeptide synthetase as described in (a) and further using any thioesterase releasing factor and/or any thioesterase type II protein. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The criteria for undue experimentation, summarized in *re Wands*, 8, USPQ2nd 1400 (Fed. Cir. 1988) are: 1) quantity of experimentation necessary, 2) the amount of direction or

guidance presented, 3) the presence and absence of working examples, 4) the nature of the invention, 5) the state of prior art, 6) the relative skill of those in the art, 7) the predictability or unpredictability of the art, and 8) the breath of the claims.

The scope of the claims, as described above, is not commensurate with the enablement provided in regard to the extremely large number of unknown dipeptide synthetases, adenylation domains, thiolation domains, condensation domains, thioesterase releasing factors, and thioesterase type II proteins required to practice the claimed method. While one could argue that the full scope of the claimed method is enabled in view of the two hybrid dipeptide synthetases disclosed by the specification, as indicated above, the specification fails to disclose (1) the structures of other Asp-Phe dipeptide synthetases, adenylation domains, thiolation domains, condensation domains, thioesterase releasing factors and thioesterase type II proteins as encompassed by the claims, (2) the critical structural elements required in any polypeptide to display Asp-Phe dipeptide synthetase activity, thioesterase type II activity or the critical structural elements required in any thioesterase releasing factor, and (3) which domains/modules (i.e. from which organisms) can be mixed to create hybrid Asp-Phe dipeptide synthetases that can be used in the claimed method. Moreover, as previously discussed, the state of the art teaches the unpredictability of isolating/making the required proteins using structural homology (i.e. sequence homology). See the teachings of Bork, Broun et al., Seffernick et al., Witkowski et al. and Van de Loo et al. already discussed. Therefore, due to the lack of relevant examples, the amount of information provided, the lack of knowledge about the structural elements required to display the desired function, and the unpredictability of the prior art in regard to isolating/making functional homologs using structural homology, one of ordinary skill in the art

would have to go through the burden of undue experimentation in order to screen and isolate those polypeptides, as encompassed by the claim, required to synthesize Asp-Phe dipeptides. Thus, Applicant has not provided sufficient guidance to enable one of ordinary skill in the art to make and use the invention in a manner reasonably correlated with the scope of the claims.

Conclusion

26. No claim is in condition for allowance.

27. Applicants are requested to submit a clean copy of the pending claims (including amendments, if any) in future written communications to aid in the examination of this application.

28. Certain papers related to this application may be submitted to Art Unit 1652 by facsimile transmission. The FAX number is (703) 308-4556. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If Applicant submits a paper by FAX, the original copy should be retained by Applicant or Applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Delia M. Ramirez whose telephone number is (703) 306-0288. The examiner can normally be reached on Monday-Friday from 8:30 AM to 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Ponnathapura Achutamurthy can be reached on (703) 308-3804. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Delia M. Ramirez, Ph.D.
Patent Examiner
Art Unit 1652

DR
September 3, 2003

REBECCA E. PROUTY
PRIMARY EXAMINER
GROUP ~~1600~~
1600